Remarks

A. Amendments to specification that track amendments in Applicants' September 5, 2003 Preliminary Amendment A

Applicants filed a Preliminary Amendment A on September 5, 2003. That amendment included several amendments to the specification. It did not, however, include clean replacement paragraphs for each of those amendments as required by 37 CFR §1.121. Thus, this Preliminary Amendment B re-submits the amendments to the specification with clean replacement paragraphs in accordance with 37 CFR §1.121. As Applicants noted the Preliminary Amendment A, these amendments do not introduce new matter. Specifically:

1. In accordance with 37 CFR §1.78 and MPEP §202.01, the first paragraph in the specification has been amended to identify the patent application to which this patent application is claiming priority.

2. The title (on page 1) and paragraphs 14, 16, 20-22, 55, 686-707, 726-729, 731, 734, 883, 1050, 1059-1061, and 1114 have been amended to replace "hydroxamate" with "hydroxamic acid". In addition, paragraph 2 and the abstract (on page 634) have been amended to indicate that the term "hydroxamic acid" includes hydroxamates. Applicants submit that these amendments simply rephrase the specification, and are therefore proper under MPEP §2163.07. They also are supported by, for example, Applicants' description of the compounds encompassed by the invention.

3. Paragraphs 696 and 707 have been amended to replace "MMP-3" with "MMP-13". This amendment corrects an obvious typographical error, and is therefore proper under MPEP §2163.07. This amendment also is supported by Applicants' specification, which, for example, repeatedly indicates that selective inhibition of MMP-2, MMP-9, and MMP-13 activity is often particularly preferred when preventing or treating the diseases listed in Paragraphs 696 and 707. *See, e.g.*, Paragraphs 691 and 702 on pages 177 and 179.

The Preliminary Amendment A also included several amendments to the claims. Applicants submit that those amendments comply with 37 CFR §1.121, and therefore have not re-submitted them in this Preliminary Amendment B.

B. Additional amendments to specification

In addition to re-submitting the amendments to the specification from Preliminary Amendment A, this Preliminary Amendment B includes various other amendments to the specification. Applicants submit these amendments also do not introduce any new matter. Specifically:

1. Paragraphs 8, 13, 15, 20, 1051, 1055, 1064, and 1112 have been amended to correct various cites. Applicants submit that these amendments correct obvious errors, and are therefore permissible under MPEP §2163.07. Applicants further submit that these amendments are supported by the cited references themselves.

2. The structure of Formula XI in paragraph 422 on page 134 has been amended to replace "-E^1-E^2-O-E^4-E^5" with "-O-E^2-O-E^5". Applicants submit that this amendment is supported by Applicants' specification at, for example, claim 308 (as originally filed).

3. The heading on page 176 at line 2 has been amended to specifically characterize the selectivities as MMP selectivities. Applicants submit that this amendment is supported by paragraphs 686-707 (on pages 176-180) that follow the heading.

4. Paragraph 727 on page 184 has been amended to include aggrecanase as a target of the compounds of this invention. Applicants submit that this amendment is supported throughout Applicants' specification. Such support includes, for example, paragraph 48 on page 20.

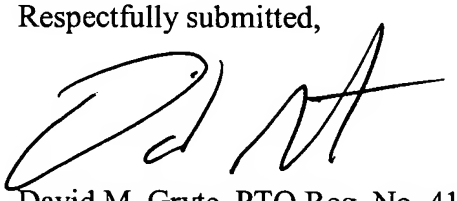
Other amendments simply rephrase the specification, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

* * * * * * * * *

Applicants request consideration on the merits of the above-referenced patent application, and submit that the pending claims are in condition for allowance. Applicants do not believe that they owe any fee in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

The Examiner is requested to call the undersigned if any questions arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,



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Appendix A
Marked-Up Version of Amendments to Specification

The title on page 1 at lines 1-2 has been amended in the following manner:

AROMATIC SULFONE **HYDROXAMIC ACIDS** ~~**HYDROXAMATES**~~ AND THEIR USE AS PROTEASE INHIBITORS

Paragraph 1 on page 1 has been amended in the following manner:

[1] This patent claims priority **as a divisional of U.S. Patent Application Serial No. 10/142,737 (filed May 10, 2002), which, in turn, claims priority** to U.S. Provisional Patent Application Serial No. 60/290,375 (filed May 11, 2001). The entire text of **each of the above-referenced applications** ~~**U.S. Provisional Patent Application Serial No. 60/290,375**~~ is incorporated by reference into this patent.

Paragraph 2 on page 1 has been amended in the following manner:

[2] This invention is directed generally to proteinase (also known as "protease") inhibitors, and, more particularly, to aromatic sulfone ~~**hydroxamates (also known as "aromatic sulfone**~~ hydroxamic acids ["] **(including hydroxamates)** that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to compositions of such inhibitors, intermediates for the syntheses of such inhibitors, methods for making such inhibitors, and methods for preventing or treating conditions associated with MMP activity and/or aggrecanase activity, particularly pathological conditions.

Paragraph 5 bridging pages 1 and 2 has been amended in the following manner:

[5] Matrix metalloproteinases, a family of zinc-dependent proteinases, make up a major class of enzymes involved in degrading connective tissue. Matrix metalloproteinases are divided into classes, with some members having several different names in common use. Examples are: MMP-1 (also known as collagenase 1, fibroblast collagenase, or EC 3.4.24.3); MMP-2 (also known as gelatinase A, 72kDa gelatinase, basement membrane collagenase, or EC 3.4.24.24), MMP-3 (also known as stromelysin 1 or EC 3.4.24.17), proteoglycanase, MMP-7

(also known as matrilysin), MMP-8 (also known as collagenase II, neutrophil collagenase, or EC 3.4.24.34), MMP-9 (also known as gelatinase B, 92kDa gelatinase, or EC 3.4.24.35), MMP-10 (also known as stromelysin 2 or EC 3.4.24.22), MMP-11 [[1 I]] (also known as stromelysin 3), MMP-12 (also known as metalloelastase, human macrophage elastase or HME), MMP- 13 (also known as collagenase 111), and MMP- 14 (also known as MT1-MMP or membrane MMP). *See, generally*, Woessner, J.F., "The Matrix Metalloprotease Family" in *Matrix Metalloproteinases*, pp.1-14 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

Paragraph 8 on page 3 has been amended in the following manner:

[8] Inhibiting TNF (and related compounds) production and action is an important clinical disease treatment. Matrix metalloproteinase inhibition is one mechanism that can be used. MMP *(e.g.,* collagenase, stromelysin, and gelatinase) inhibitors, for example, have been reported to inhibit TNF-α release. *See, e.g.,* Gearing et al. *Nature*, 370, [[376,]] 555-557 (1994). *See also*, McGeehan et al. ~~*See also*~~, *Nature*, 370 [[376]], 558-561 (1994). MMP inhibitors also have been reported to inhibit TNF-α convertase, a metalloproteinase involved in forming active TNF-α. *See, e.g.,* WIPO Int'l Pub. No. WO 94/24140. *See also*, WIPO Int'l Pub. No. WO 94/02466. *See also*, WIPO Int'l Pub. No. WO 97/20824.

Paragraph 13 on page 4 has been amended in the following manner:

[13] A wide variety of thiol compounds have been reported to inhibit MMPs. *See, e.g.,* WO 95/13289 ~~W095/12389~~. *See also*, W0 96/11209. *See also*, U.S. Patent No. 4,595,700. *See also*, U.S. Patent No. 6,013,649 ~~6.013,649~~.

Paragraph 14 on page 4 has been amended in the following manner:

[14] A wide variety of hydroxamic acid ~~hydroxamate~~ compounds also have been reported to inhibit MMPs. Such compounds reportedly include hydroxamic acids ~~hydroxamates~~ having a carbon backbone. *See, e.g.,* WIPO Int'l Pub. No. *WO* 95/29892. *See also*, WIPO Int'l Pub. No. WO 97/24117. *See also*, WIPO Int'l Pub. No. WO 97/49679. *See also*, European Patent No. EP 0 780 386. Such compounds also reportedly include hydroxamic acids ~~hydroxamates~~ having peptidyl backbones or peptidomimetic backbones. *See, e.g*, WIPO

Int'l Pub. No. WO 90/05719. *See also*, WIPO Int'l Pub. No. WO 93/20047. *See also*, WIPO Int'l Pub. No. WO 95/09841. *See also*, WIPO Int'l Pub. No. WO 96/06074. *See also*, Schwartz et al., Progr. *Med. Chem.*, 29:271-334(1992). *See also*, Rasmussen et al., *PharmacoL Ther.*, 75(l): 69-75 (1997). *See also*, Denis et al., *Invest New Drugs*, 15 **[[(3)]]**: 175-185 (1997). Various piperazinylsulfonylmethyl **hydroxamic acids** ~~**hydroxamates**~~ and piperidinylsulfonylmethyl **hydroxamic acids** ~~**hydroxamates**~~ have additionally been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ have been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 99/25687. *See also*, WIPO Int'l Pub. No. WO 00/50396. *See also*, WIPO Int'l Pub. No. WO 00/69821.

Paragraph 15 bridging pages 4 and 5 has been amended in the following manner:

[15] It is often advantageous for an MMP inhibitor drug to target a certain MMP(s) over another MMP(s). For example, it is typically preferred to inhibit MMP-2, MMP-3, MMP-9, and/or MMP-13 (particularly MMP-13) when treating and/or preventing cancer, inhibiting of metastasis, and inhibiting angiogenesis. It also is typically preferred to inhibit MMP-13 when preventing and/or treating osteoarthritis. *See, e.g.*, Mitchell et al., J *Clin. Invest.*, 97**(3)**:761-768 (1996). *See also*, Reboul et al., *J Clin. Invest.*, 97**(9)**:2011-2019 (1996). Normally, however, it is preferred to use a drug that has little or no inhibitory effect on MMP-1 and MMP-14. This preference stems from the fact that both MMP-1 and MMP-14 are involved in several homeostatic processes, and inhibition of MMP-1 and/or MMP-14 consequently tends to interfere with such processes.

Paragraph 16 on page 5 has been amended in the following manner:

[16] Many known MMP inhibitors exhibit the same or similar inhibitory effects against each of the MMPs. For example, batimastat (a peptidomimetic **hydroxamic acid** ~~**hydroxamate**~~) has been reported to exhibit IC_{50} values of from about 1 to about 20 nM against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat (another peptidomimetic **hydroxamic acid** ~~**hydroxamate**~~) has been reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum similar to batimastat, except that Marimastat reportedly

exhibited an IC_{50} value against MMP-3 of 230 nM. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(l): 69-75 (1997).

Paragraph 20 on page 6 has been amended in the following manner:

[20] Various **hydroxamic acid** ~~**hydroxamate**~~ compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No. EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. **WO 99/09000** ~~**WO 00/09000**~~. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

Paragraph 21 on page 6 has been amended in the following manner:

[21] In view of the importance of **hydroxamic acid** ~~**hydroxamate**~~ compounds in the prevention or treatment of several pathological conditions and the lack of enzyme specificity exhibited by two of the more potent MMP-inhibitor drugs that have been in clinical trials, there continues to be a need for **hydroxamic acids** ~~**hydroxamates**~~ having greater enzyme specificity (preferably toward MMP-2, MMP-9, MMP- 13, and/or aggrecanase (particularly toward MMP-13 in some instances, toward both MMP-2 and MMP-9 in other instances, and aggrecanase in yet other instances), while exhibiting little or no inhibition of MMP-1 and/or MMP-14. The following disclosure describes **hydroxamic acid** ~~**hydroxamate**~~ compounds that tend to exhibit such desirable activities.

Paragraph 22 on page 7 has been amended in the following manner:

[22] This invention is directed to **hydroxamic acid** ~~**hydroxamate**~~ compounds (and salts thereof) that inhibit pathological protease activity (particularly compounds that inhibit MMP-2, MMP-9, MMP- 13, and/or aggrecanase activity), while generally exhibiting relatively little or no inhibition against MMP-1 and MMP-14 activity. This invention also is directed to a method for inhibiting MMP activity and/or aggrecanase activity, particularly pathological MMP and/or aggrecanase activity. Such a method is particularly suitable to be used with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees. etc.), companion animals (*e.g.*,

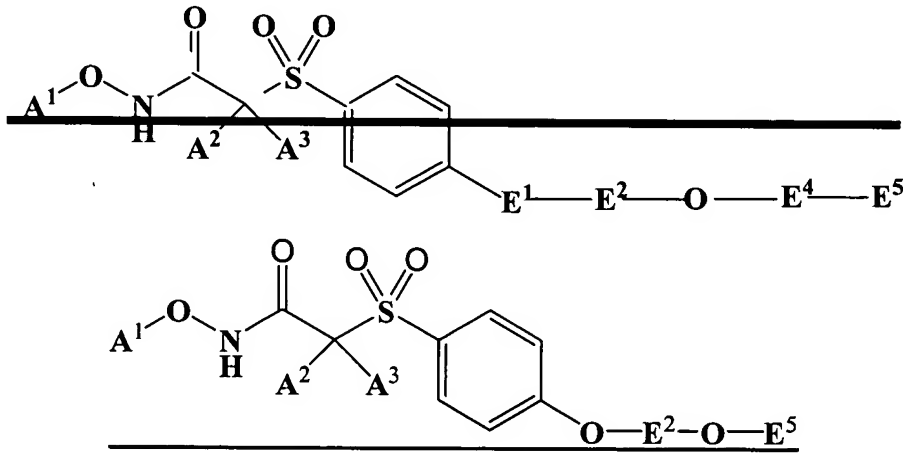
dogs, cats, horses, **[[.]]** etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

Paragraph 55 on page 21 has been amended in the following manner:

[55] In accordance with this invention, it has been found that certain aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ tend to be effective for inhibiting MMPs, particularly those associated with excessive (or otherwise pathological) breakdown of connective tissue. Specifically, Applicants have found that these **hydroxamic acids** ~~**hydroxamates**~~ tend to be effective for inhibiting proteases (particularly MMP-2, MMP-9, MMP- 13, other MMP's associated with pathological conditions, and/or aggrecanase) that are often particularly destructive to tissue if present or generated in abnormally excessive quantities or concentrations. Moreover, Applicants have discovered that these **hydroxamic acids** ~~**hydroxamates**~~ tend to be selective toward inhibiting pathological protease activity, while avoiding excessive inhibition of other proteases (particularly MMP-1 and/or MMP-14) that are typically essential to normal bodily function *(e.g.,* tissue turnover and repair).

Paragraph 422 on page 134 has been amended in the following manner:

[422] In some embodiments of this invention, the compound has a structure corresponding to Formula XI:



XI

The heading on page 176 at line 2 has been amended in the following manner:

A-2. Preferred ***MMP*** *Selectivities*

Paragraph 686 on page 176 has been amended in the following manner:

[686] The **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an inhibitory activity against MMP-1 or MMP-14 that is substantially less than its inhibitory activity against MMP-2, MMP-9, or MMP-13. In other words, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an in inhibition constant (K_i) against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its inhibition constant(s) against at least one of MMP-1 and MMP-14. The inhibition constant of à compound or salt thereof may be determined using an *in vitro* inhibition assay, such as the K_i assay described below in Examples 55-89.

Paragraph 687 on page 176 has been amended in the following manner:

[687] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

Paragraph 688 on page 176 has been amended in the following manner:

[688] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

Paragraph 689 bridging pages 176 and 177 has been amended in the following manner:

[689] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Paragraph 690 on page 177 has been amended in the following manner:

[690] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Paragraph 691 on page 177 has been amended in the following manner:

[691] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 692 on page 177 has been amended in the following manner:

[692] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

Paragraph 693 on page 177 has been amended in the following manner:

[693] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

Paragraph 694 bridging pages 177 and 178 has been amended in the following manner:

[694] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Paragraph 695 on page 178 has been amended in the following manner:

[695] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed

that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Paragraph 696 on page 178 has been amended in the following manner:

[696] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-**13** **[[3]]** that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 697 on page 178 has been amended in the following manner:

[697] The activity and selectivity of a **hydroxamic acid** ~~**hydroxamate**~~ compound or salt may alternatively be determined using an *in vitro* IC_{50} assay, such as the IC_{50} assay described below in Examples 55-89. In that instance, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its IC_{50} value(s) against at least one of MMP-1 and MMP-14.

Paragraph 698 on page 178 has been amended in the following manner:

[698] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

Paragraph 699 bridging pages 178 and 179 has been amended in the following manner:

[699] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

Paragraph 700 on page 179 has been amended in the following manner:

[700] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Paragraph 701 on page 179 has been amended in the following manner:

[701] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Paragraph 702 on page 179 has been amended in the following manner:

[702] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably

no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 703 on page 179 has been amended in the following manner:

[703] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

Paragraph 704 bridging pages 179 and 180 has been amended in the following manner:

[704] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

Paragraph 705 on page 180 has been amended in the following manner:

[705] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Paragraph 706 on page 180 has been amended in the following manner:

[706] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Paragraph 707 on page 180 has been amended in the following manner:

[707] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-**13** **[[3]]** that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Paragraph 710 on page 181 has been amended in the following manner:

[710] Pharmaceutically-acceptable acid addition salts of the compounds of this invention may be prepared from an inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic acid, ~~**hydroionic**~~ **hydroiodic**, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, ~~**heterocyclyl**~~ **heterocyclic**, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), ~~**methanesulfonate,**~~ ethanesulfonate, benzenesulfonate, pantothenate,

~~toluenesulfonate,~~ 2-hydroxyethanesulfonate, ~~sufanilate~~ sulfanilate, cyclohexylaminosulfonate, algenic acid, [[b-]] β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, ~~bisulfate,~~ butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, ~~hemisulfate,~~ heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, ~~persulfate,~~ 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Paragraph 711 bridging pages 181 and 182 has been amended in the following manner:

[711] Pharmaceutically-acceptable base addition salts of the compounds of this invention include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other ~~physiological~~ physiologically acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from ~~tertiary~~ amines ~~and quaternary amine salts~~, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, ~~choline,~~ diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C_1-C_6) halides *(e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates *(e.g.,* dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides *(e.g.,* decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), aralkyl halides *(e.g.,* benzyl and phenethyl bromides), and others.

Paragraph 726 bridging pages 183 and 184 has been amended in the following manner:

[726] A wide variety of methods may be used alone or in combination to administer the hydroxamic acids ~~hydroxamates~~ and salt thereof described above. For example, the hydroxamic acids ~~hydroxamates~~ or salts thereof may be administered orally, parenterally, by inhalation spray, rectally, or topically.

Paragraph 727 on page 184 has been amended in the following manner:

[727] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s) **or aggrecanase**. The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly preferred target. The preferred total daily dose of the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

Paragraph 728 on page 184 has been amended in the following manner:

[728] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof employed; whether a drug delivery system is utilized; and whether the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and, therefore, can deviate from the preferred dosage regimen set forth above.

Paragraph 729 on page 184 has been amended in the following manner:

[729] This invention also is directed to pharmaceutical compositions comprising a **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof described above, and to methods for making pharmaceutical compositions (or medicaments) comprising a **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof described above.

Paragraph 731 on page 185 has been amended in the following manner:

[731] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof are ordinarily combined with one or more adjuvants. If administered *per os*, the **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof can be mixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

Paragraph 734 on page 185 has been amended in the following manner:

[734] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, com oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

Paragraph 781 on page 194 has been amended in the following manner:

[781] The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated, or ~~aryl (*i.e.*, "~~ heteroaryl [["")]] ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

Paragraph 782 bridging pages 194 and 195 has been amended in the following manner:

[782] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofurnayl, tetradydrofurnayl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), **and [[or]]** 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl **and [[or]]** 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, **and [[or]]** 1,3,4-dioxazolyl), ~~**oxathiazolyl, oxathiolyl,**~~ oxathiolanyl, pyranyl (including 1,2-pyranyl **and [[or]]** 1,4-pyranyl), dihydropyranyl, pyridinyl ~~**(also known as "azinyl")**~~, piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), **and [[or]]** pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, **and [[or]]** 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl **and [[or]]** p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl **and [[or]]** 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl **and [[or]]** 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Paragraph 783 bridging pages 195 and 196 has been amended in the following manner:

[783] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, ~~**naphthyridinyl,**~~

pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, **[[or]]** pyrido[4,3-b]-pyridinyl**, and naphthyridinyl**), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl ~~(also known as "isobenzazolyl" or "pseudoisoindolyl")~~, indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") **and [[or]]** isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, ~~quinazolinyl,~~ benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") **and [[or]]** quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including **chromenyl and isochromenyl** ~~"chromanyl" or "isochromanyl"~~), benzothiopyranyl (also known as **"thiochromenyl"** ~~"thiochromanyl"~~), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", or "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl**[[ ]]**, 1,4,2-benzoxazinyl**[[ ]]**, 2,3,1-benzoxazinyl**[[ ]]**, **and [[or]]** 3,1,4-benzoxazinyl**[[ ]]**), benzisoxazinyl (including 1,2-benzisoxazinyl **and [[or]]** 1,4-benzisoxazinyl), tetrahydroisoquinolinyl**[[ ]]**, carbazolyl, xanthenyl, and acridinyl.

Paragraph 784 on page 196 has been amended in the following manner:

[784] The term **"2-fused-ring"** ~~"2-fused'ring"~~ heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or **heteroaryl** ~~aryl heterocyclyl~~ containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, ~~naphthyridinyl,~~ pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Paragraph 785 on page 196 has been amended in the following manner:

[785] The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as ~~**pyridyl, pyrazyl**~~ **pyridinyl, pyrazinyl**, pyrimidinyl, **[[and]]** pyridazinyl**, and 1,3,5-, 1,2,4-, and 1,2,3-triazinyl**; 5-membered ring substituents such as ~~**1,3,5-, 1,2,4- or 1,2,3-tiiazinyl, imidazyl**~~ **imidazolyl**, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as ~~**1,2-, 1,4-, 2,3- and 2, 1-benzopyronyl,**~~ quinolinyl, isoquinolinyl, ~~**cinnolinyl, quinazolinyl,**~~ and 1,4-benzoxazinyl **(including cinnolinyl and quinazolinyl)**.

Paragraph 787 bridging pages 197 and 198 has been amended in the following manner:

[787] An aryl or heteroaryl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonyl, aminoalkyl, alkyl, alkylthio, carboxyalkylthio, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkoxy, alkoxyalkylthio, alkoxycarbonylalkylthio, carboxyalkoxy, alkoxycarbonylalkoxy, carbocyclyl, carbocyclylalkyl, carbocyclyloxy, carbocyclylthio, carbocyclylalkylthio, carbocyclylamino, carbocyclylalkylamino, carbocyclylcarbonylamino, carbocyclylcarbonyl, carbocyclylalkyl, ~~**carbonyl,**~~ carbocyclylcarbonyloxy, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, carbocyclyloxyalkoxycarbocyclyl, carbocyclylthioalkylthiocarbocyclyl, carbocyclylthioalkoxycarbocyclyl, carbocyclyloxyalkylthiocarbocyclyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylthio, heterocyclylalkylthio, heterocyclylamino, heterocyclylalkylamino, heterocyclylcarbonylamino, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, heterocyclyloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylalkoxycarbonyl, heterocyclyloxyalkoxyheterocyclyl,

heterocyclylthioalkylthioheterocyclyl, heterocyclylthioalkoxyheterocyclyl, and heterocyclyloxyalkylthioheterocyclyl. More typically, an aryl or heteroaryl may, for example, optionally be substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonyl, amino-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-alkylthio, carboxy-C_1-C_6-alkylthio, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkylthio, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkylthio, carboxy-C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, aryl, aryl-C_1-C_6-alkyl, aryloxy, arylthio, aryl-C_1-C_6-alkylthio, arylamino, aryl-C_1-C_6-alkylamino, arylcarbonylamino, arylcarbonyl, aryl-C_1-C_6-alkylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, aryloxy-C_1-C_6-alkoxyaryl, arylthio-C_1-C_6-alkylthioaryl, arylthio-C_1-C_6-alkoxyaryl, aryloxy-C_1-C_6-alkylthioaryl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyloxy, cycloalkylthio, cycloalkyl-C_1-C_6-alkylthio, cycloalkylamino, cycloalkyl-C_1-C_6-alkylamino, cycloalkylcarbonylamino, cycloalkylcarbonyl, cycloalkyl-C_1-C_6-alkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, cycloalkyl-C_1-C_6-alkoxycarbonyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryloxy, heteroarylthio, heteroaryl-C_1-C_6-alkylthio, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, heteroarylcarbonylamino, heteroarylcarbonyl, heteroaryl-C_1-C_6-alkylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, and heteroaryl-C_1-C_6-alkoxycarbonyl. Here, one or more hydrogen bound to a carbon in any such substituent may, for example, optionally be replaced with halogen. In addition, the cycloalkyl, aryl, and heteroaryl are typically single-ring substituents containing 3 to 6 ring atoms, and more typically 5 or 6 ring atoms.

Paragraph 883 on page 228 has been amended in the following manner:

[883] **Part C.** The product from **Part B** (530 mg, 0.91 mmol) was dissolved in 4N HCl in dioxane (5 mL) and methanol (1 mL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 360 mg of the desired **hydroxamic acid** ~~**hydroxamate**~~. Purification by reverse phase HPLC afforded 270 mg (59%) of the title

compound. ESMS m/z = 504 $[M+H]^+$. HRMS calculated for $C_{25}H_{28}N_2O_7S$: 501 . 1695 $[M+H]^+$, found: 501. 1689.

Paragraph 1050 on page 286 has been amended in the following manner:

[1050] Several **hydroxamic acids** ~~**hydroxamates**~~ and salts thereof were analyzed in *in vitro* assays to determine their ability to inhibit the MMP cleavage of peptide substrates. Inhibition (K_i) and IC_{50} constants were calculated from the assayed ~~**hydroxamate**~~ **hydroxamic acid**-MMP interactions.

Paragraph 1051 on page 287 has been amended in the following manner:

[1051] Human recombinant MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 were used in this assay. All enzymes were prepared in Assignee's laboratories following usual laboratory procedures. Protocols for the preparation and use of these enzymes are available in the scientific literature. *See, e.g., Enzyme Nomenclature* (Academic Press, San Diego, CA, 1992) (and the citations therein). *See also*, **[[Frije]]** **Freije,** et al., *J Biol. Chem.*, **[[26]]** **269**(24), 16766-**16773** **[[73]]** (1994).

Paragraph 1055 on page 287 has been amended in the following manner:

[1055] The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V.A. Luckow, "Insect Cell Expression Technology," *Protein Engineering: Principles and Practice,* pp. 183-218 (edited by J.L. Cleland et al., Wiley-Liss, Inc., 1996). The expressed proenzyme was first purified over a heparin agarose column, and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67**(8)**, 4566-79 (1993). *See also*, O'Reilly et al, *Baculovirus Expression Vectors: A Laboratory Manual* (W.H. Freeman and Co., New York, NY, 1992). *See also*, King et al., *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London, England, 1992).

Paragraph 1059 on page 288 has been amended in the following manner:

[1059] The stock solutions of the assayed **hydroxamic acids** ~~**hydroxamates**~~ (or salts thereof) were prepared in 1% dimethyl sulfoxide (DMSO). These stock solutions were diluted in Buffer A (100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, 0.05% polyoxyethylene 23 lauryl ether, pH 7.5) to obtain solutions with different **hydroxamic acid** ~~**hydroxamate**~~ concentrations, *i.e.*, assay solutions with different concentrations of the assayed MMP inhibitory compound. The experiment controls contained the same amount of Buffer A/DMSO as the assayed sample, but contained no **hydroxamic acid** ~~**hydroxamate**~~ (or salt thereof).

Paragraph 1060 bridging pages 288 and 289 has been amended in the following manner:

[1060] The assays from which the IC_{50} determinations were made were performed as follows. The MMPs were activated with either trypsin or APMA (4-aminophenylmercuric acetate, Sigma Chemical, St. Louis, MO). The assayed **hydroxamic acid** ~~**hydroxamate**~~ samples were incubated in Microfluor™ White Plates (Dynatech, Chantilly, VA) and analyzed on a Perkin Elmer L550 plate reader (Norwalk, CT). The excitation wavelength was 328 nm, and the emission wavelength – 415 nm. All samples (assayed **hydroxamic acids** ~~**hydroxamates**~~ and controls) were incubated in separate plates at room temperature in the presence of 4 μM of MMP substrate (I). As stated in the previous paragraph, samples containing varying concentrations of the same assayed **hydroxamic acid** ~~**hydroxamate**~~ were prepared. Inhibition was measured as a reduction in fluorescent intensity as a function of MMP inhibitor concentration.

Paragraph 1061 on page 289 has been amended in the following manner:

[1061] The assays from which the K_i determinations were made were performed as follows. The assayed **hydroxamic acid** ~~**hydroxamate**~~ samples were incubated in separate wells of untreated white polystyrene plates (Nunc Nalgene International, Rochester, NY), and analyzed on a Tecan SpectraFlour Plus plate reader. The excitation wavelength was 330 nm, and the emission wavelength – 420 nm. All samples (assayed **hydroxamic acids** ~~**hydroxamates**~~ and controls) were incubated in separate plate wells at room temperature for 1 hr in the presence of 4 μM of MMP substrate (II). In the absence of MMP inhibitory activity, substrate II was cleaved

at the Gly-Leu bond resulting in an increase of relative fluorescence. Inhibition was observed as a reduced rate of this increase in relative fluorescence. The various **hydroxamic acids** ~~**hydroxamates**~~ were analyzed using a single low enzyme concentration with a single substrate concentration fixed at or below the K_m. This protocol is a modification of method by Knight et al., *FEBS Lett.*, 296(3), 263-266 (1992). Apparent inhibitory constants were determined by non-linear regression of reaction velocity as a function of inhibitor and enzyme concentration using Morrison's equation, as described by Kuzmic, Anal. Biochem. 286, 45-50 (2000). Modifications were made in the non-linear regression method to allow a common control reaction rate and effective enzyme concentration to be shared between all dose-response relationships on a given assay plate. Since the substrate concentration was chosen to be at or below the K_m, the apparent K_i's from this analysis were reported as K_i's without correction for the influence of substrate.

Paragraph 1064 on page 291 has been amended in the following manner:

[1064] The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, "A Model of Angiogenesis in the Mouse Cornea" ~~; Kenyon,BM, et al.~~, Investigative Ophthalmology & Visual Science, ~~July 1996,~~ Vol. 37, No. 8, **pp. 1625-1632 (July 1996)**.

Paragraph 1112 bridging pages 296-298 has been amended in the following manner:

[1112] Another assay for measuring aggrecanase inhibition is reported in WIPO Int'l Publ. No. WO 00/59874. That assay reportedly uses active aggrecanase accumulated in media from stimulated bovine cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), or other stimuli. To accumulate BNC aggrecanase in culture media, cartilage reportedly is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-β for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. To decrease the amounts of matrix metalloproteinases released into the media during aggrecanase

accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, et al., *Biochem J*, **[[306]] 305(3)**:799-804 (1995)). This antibody reportedly recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody reportedly recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Only products produced upon cleavage by aggrecanase reportedly are detected. Kinetic studies using this assay reportedly yield a Km of 1.5+/-0.35 μM for aggrecanase. To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water, or other solvents and diluted to appropriate concentrations in water. Drug (50 μL) is added to 50 μL of aggrecanase-containing media and 50 μL of 2 mg/ml aggrecan substrate and brought to a final volume of 200 μL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA, and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background. Removal of the glycosaminoglycan side chains from aggrecan reportedly is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 μg GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 μg GAG) and keratanase II (0.002 units/10 μg GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μL of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and

aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

Paragraph 1114 on page 298 has been amended in the following manner:

[1114] Additional **hydroxamic acid** ~~**hydroxamate**~~ compounds (and salts thereof) can be prepared by one skilled in the art using methods similar to those described in **Examples 1-54** alone or in combination with techniques well known in the art. Such compounds include, for example, the compounds summarized in the following **Table 7**. **Table 7** also summarizes *in vitro* MMP inhibition results obtained by Applicants with the listed **hydroxamic acids** ~~**hydroxamates**~~. As with **Table 5**, all *in vitro* K_i and IC_{50} results in **Table 7** are given in nM units. The Ki measurements are in parenthesis.

The abstract on page 634 has been amended in the following manner:

This invention is directed to aromatic sulfone ~~**hydroxamates (also known as "aromatic sulfone**~~ hydroxamic acids ~~**"]**~~ **(including hydroxamates)** and salts thereof that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to a prevention or treatment method that comprises administering such a compound or salt in an MMP-inhibiting and/or aggrecanase-inhibiting effective amount to an animal, particularly a mammal having (or disposed to having) a pathological condition associated with MMP and/or aggrecanase activity.

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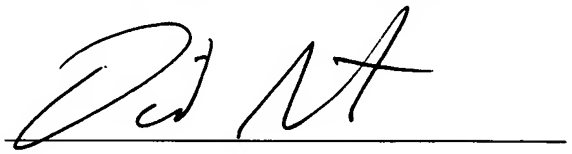

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